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08/405,454

03/15/1995

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| EXAMINER |
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WOODWARD, MICHAEL P

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1637

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11/16/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**RECEIVED**  
Wolf, Greenfield & Sacks, P.C.

NOV 18 2010

Docketed ☒ Already Docketed \_\_\_\_\_  
Not Required ☒  
Initials 1st MTS 2nd \_\_\_\_\_

MTS

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|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 08/405,454             | SULLIVAN ET AL.     |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | MP WOODWARD            | 1637                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 June 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 40-42 and 54-72 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 40-42 and 50-72 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)✓           | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>June 30, 2010</u> . ✓   | 6) <input type="checkbox"/> Other: _____                          |

Applicants in this case appealed the June 15, 2009, decision of the Board of Patent Appeals and Interferences ("Board") to the District Court for the District of Columbia ("District Court"). On May 10, 2010, the United States Patent and Trademark Office ("USPTO") filed an unopposed motion to have the case remanded to the USPTO for further consideration of new evidence.

On May 11, 2010, the District Court granted the motion for remand.

The examiner interprets the remand to require that consideration of the new evidence compels consideration of the prosecution history of the application.

On June 29, 2010 applicant filed a response which (1) amended withdrawn claim 54 and presented new claims 57-72, (2) included an Information Disclosure Statement, (3) proffered evidence of commercial success and (4) included the Declaration of Dart.

#### **Amendment of June 29, 2010**

The examiner notes applicant's request for an interview. However, the issues involved in the prosecution of this application will be best handled at this point in time by setting forth the issues remaining following a consideration of the evidence present in the file wrapper. Once the issues are set forth the examiner is amenable to an Interview so as to facilitate resolution.

The examiner works a part-time schedule and is also hoteling from Kingwood, Texas. However, it is anticipated that advantage can be taken of video conferencing so as to facilitate resolution of the issues.

### **Claim Amendments**

Page 7 (Amendment June 29, 2010)

The language of new claims 56 and 57 has support in the specification as originally filed.

The language of new claim 58 has support in the specification as originally filed.

The language of new claim 59 has support in the specification as originally filed.

The language of new claims 60-62 has support in the specification as originally filed.

Page 8 (Amendment June 29, 2010)

The language of new claim 63 has support in the specification as originally filed.

The language of new claims 64 and 65 has support in the specification as originally filed.

The language of new claims 66-68 has support in the specification as originally filed.

The language of new claim 69 has support in the specification as originally filed.

Page 9 (Amendment June 29, 2010)

The language of new claim 70 has support in the specification as originally filed.

The language of new claim 71 has support in the specification as originally filed.

The language of new claim 72 has support in the specification as originally filed.

That the language has support is not necessarily an acquiescence that the claim as a whole has support in the specification as originally filed.

### **Request for Rejoinder Upon Indication of Allowable Claims**

The request is acknowledged.

### **Procedural History**

Applicant's summary of the procedural history is acknowledged.

Following remand, the Board of Patent Appeals & Interferences upheld the extant grounds of rejection on the basis of its original holding and in light of its evaluation of the prima facie obviousness in view of Applicant's Declarations. Applicant appealed the latest decision to the District Court for the District of Columbia. In its Complaint Appellant indicated in paragraph 24 that it had

evidence of commercial success which had not been considered by the USPTO (paragraph 24). The USPTO requested that the application be remanded to the USPTO which request was granted.

It is the examiner's understanding that in complying with the remand that he is to evaluate the evidence of commercial success as well as any additional evidence newly supplied by applicant. It is further understood that such a consideration permits reconsideration of Applicant's previously filed Declarations and arguments considering the grounds of rejection extant at the time the application went to the District Court.

**The USPTO has not established a prima facie case of obviousness**

**A. The Federal Circuit did NOT find a prima facie case had been established**

The examiner appreciates the subtlety of applicant's remarks regarding whether or not the Federal Circuit decision actually held that a prima facie case of obviousness had been made. Regardless, it was clearly stated that the USPTO had not met its burden with respect to applicant's rebuttal of the obviousness rejections.

**B. The USPTO has NOT established a prima facie case**

The following is in response to applicant's remarks.

**Reconsideration of Prior Grounds of Rejection**

40. (Previously Presented) An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically

acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus.

At the time of the remand the following rejections had been affirmed by the Board:

Claims 40-42 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan in view of Coulter.

Claims 40-42 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan in view of Coulter, Smith and Stedman's.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

*Scope and Content of the prior art.*

While Sullivan (1987, IDS 06/29/2010) was not of record during the prior prosecution of the claims it is being relied on here to establish historical context.

Sullivan (1987) reviews much of what was known regarding antivenoms as of 1987. It is relied on herein in so far as its teachings relate to the state of the art as of October 9, 1984.

- 1) Sullivan notes that antivenin had been commercially available since 1947 from Wyeth Laboratories. The source for the antivenin was serum from hyperimmunized horses.
- 2) Commercial production involved ammonium sulfate precipitation of hyperimmune serum, enzyme digestion of hyperimmune serum or packaging of unprocessed hyperimmune serum.
- 3) The presence of normal serum proteins in the available preparations often resulted in serious side effects.
- 4) In 1982 Sullivan et al. reported the first affinity purification of the active antibodies in horse serum-IgG(T).
- 5) Successful immunotherapy requires that the "antivenin must drastically alter the pharmacokinetics of the venom proteins to be effective. (p 943, top of left column)" Sullivan indicates that the pharmacokinetics of crotalid venom and antivenin had not been determined. Sullivan cites to studies done with scorporin toxin

With regard to point 3) Sullivan does not describe the preparations of enzymatically digested hyperimmune serum with regard to the products present. However, the Dart Declaration ¶30 and the Russell Declaration ¶¶24 & 25 explain that they resulted from pepsin treatment of the hyperimmune serum. Pepsin digestion cleaves IgG such that Fc chains result along with F(ab)<sub>2</sub>. The instant specification at page 4 discloses that certain of the pepsin digested preparations are further purified by ammonium sulfate precipitation.

With regard to point 2) Sullivan et al. (1982) and Sullivan et al. (1983) report that affinity purification, acrylamide coupled venom proteins constituted the matrix, resulted in preparations which were effective to neutralize snake venom. The immunoelectrophoresis results indicated that the affinity purified antibodies were substantially free of other serum proteins and predominantly IgG(T).

These results are consistent with the activity of venom resulting from the polypeptides present therein and the ability of antibodies to effect neutralization. In addition, they suggest that venom activity does not result from small molecules

present in venom, and that neutralization results from antibody activity rather than other than proteins present.

The Dart Declaration ¶¶ 30 & 31, the Russell Declaration ¶ 29, the Sullivan Declaration ¶ 6 and the Smith Declaration ¶ 9 each attribute the neutralization activity as resulting from binding of the antibody combining sites with determinants on the venom proteins. One infers from this attribution that the Declarants viewed the Fc portion of the antibodies as not being involved in neutralizing activity. But, at the time of the invention, there was no evidence which clearly established that no role was played by the Fc portion. This is admittedly a fine point but it is pertinent to other arguments made by the Declarants, which remarks will be discussed in what follows.

Sullivan's perspective is that of an expert in the field of antivenom research and treatment. This is a cautionary statement in that expert's are frequently viewed as persons having more than ordinary skill. Nonetheless his statements would appear to define the scope of the art as including what was known at the time of the invention regarding the clinical use of antivenoms in treating snakebite and the development of alternative antivenoms. The scope of the art extends into the area of immunoglobulin structure and activity to the extent that it is relevant to antivenom activity.

In the abstract one could view the claimed compositions as falling within the immunoassay art. In this regard the scope of the art would include the role of Fab fragments as immunoassay reagents and the reasons for replacing existing reagents with Fabs. But, this consideration would still need to be set in the context of the detection of snakebite components rather than the larger field of immunoassays.

*Ascertaining the differences between the prior art and the claims at issue*

The art currently of record including that cited in the Declarations previously filed and that relied upon in previous grounds of rejection do not teach the

production of a Fab fragment antivenom from a polyclonal preparation of antivenom against any genus of snakes. The antivenoms of the prior art appear to have consisted of partially purified IgG or partially purified F(ab)<sub>2</sub> obtained from such antivenoms. Sullivan had prepared a purified IgG fraction from equine serum which had antivenom activity prior to the invention. In the immunoassay art Coulter et al. had disclosed the use of Fab fragments directed against the textilotoxin component of *Pseudonaja textilis* venom. Their results also indicated that the Fab preparation had textilotoxin neutralizing activity when co-administered in vivo.

*Resolving the level of ordinary skill in the pertinent art*

Resolution involves much hindsight. It often centers on ascertaining how the person of ordinary skill in the art at the time the invention was made would have understood and applied the teachings of the prior art. Critically, one needs to attempt to achieve an interpretation of the art as seen through PHOSITA and not that which results from knowledge of the invention or that of someone other than PHOSITA.

In the instant application several declarations from practitioners in the art have been submitted. Each of the declarant's either self-identifies as an expert or is an inventor. In this regard their statements are not necessarily those of PHOSITA and the declarations have been evaluated keeping this in mind.

In the following analysis the examiner's comments are in Times Roman and the passages from the declaration in Arial. The examiner OCR'd the declarations and has made every attempt to insure that no errors resulted.

3. From 1985 to 1987, I was a Clinical Toxicology Fellow at the University of Arizona Health Sciences Center. My fellowship director was Dr. John B. Sullivan, and I worked there with Dr. Findlay E. Russell, who are the two inventors of this Application.

12. The antivenom field is relatively small, and I consider myself to be an expert on the topic. I also consider myself to have been one of ordinary skill in the field as of October 9, 1984. At that time I was over 3 years into my career as an M.D., including one year as a Resident in Emergency Medicine at the University of Arizona Health Sciences Center, whose Emergency Room treats as many snake bite victims as any other Emergency Room in the United States. I was also preparing to start my Fellowship in Clinical Toxicology.

Paragraph 12 asserts that he had ordinary skill in the field as of October 9, 1984. Evidently the basis for this assertion relates to his experience treating snakebites in his medical career. However, while treating snake bite may require knowledge of when treatment is effective and what potential side effects are attendant thereto it does not necessarily require an understanding of the molecular mechanisms and biological interactions involved.

13. I have been retained as a testifying expert by Wolf Greenfield & Sacks, the law firm representing the assignee Protherics, Inc. in this matter. The Rocky Mountain Poison and Drug Center is being paid at the rate of \$500 per hour for my time spent reviewing materials, consulting, and preparing this declaration. I have no financial interest in whether a patent issues from this application.

Paragraph 13 clouds the ensuing discussion as it makes it difficult to discern whether the remarks are those of an expert or those of one of ordinary skill in the art at the time the invention was made. In fairness, the examiner has to guard against the extraordinary ability of hindsight to facilitate conclusions on both the part of declarant and the examiner.

14. I have read the Decision on Appeal dated June 15, 2009. [Ex. 2.] I disagree with its conclusion that one of ordinary skill in the art would have been motivated to prepare an antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and a pharmaceutically acceptable carrier, with a reasonable expectation that the composition would neutralize the lethality of the venom of a snake of the *Crotalus* genus. [Ex. 2 at p. 16, second full paragraph; p. 16, last paragraph, through page 17, first full paragraph.]

15. I first note that the Decision bases its conclusion on the assertion that the Fab teachings of the Coulter et al. article [Ex. 3] would have lead one of ordinary skill in the art to prepare Fab fragments of the affinity-purified antibodies of the Sullivan et al. article [Ex. 4] because the Fab fragments would be expected to have improved sensitivity in assays. [Ex. 2 at p. 16, first full paragraph.] I simply do not understand how this is relevant to the claimed invention, which I understand is:

40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus.

16. The Decision seems to ignore that this claim concerns an antivenom, not an antibody for an immunoassay. The Decision's posited immunoassay reagent would not be an "antivenom." It would, not be a "pharmaceutical composition." It certainly would not be used by any clinician "for treating a snakebite victim." And no clinician would reasonably expect such an immunoassay reagent to "neutralize the lethality of the venom of a snake of the *Crotalus* genus."

17. It has been explained to me that the Decision refused to consider these elements of the claimed invention based on some legal analysis that is beyond my training and expertise. Regardless of any legal analysis, as one of at least ordinary skill in the art, I read claim 40 as requiring an in vivo purpose, use, property, and effect. Nothing in the combined teachings of the Sullivan et al. and Coulter et al. articles would have provided a reasonable expectation of "neutralizing the lethality of the venom of a snake of the *Crotalus* genus" with an "antivenom pharmaceutical composition" "for treating a snakebite victim" comprising Fab fragments that bound to the venom of a snake of the *Crotalus* genus.

It is unclear what was explained to Dart. Moreover, he is not one of ordinary skill in the art of claim interpretation. It appears to be that the Board took the position that the wherein clause was a statement of intended use rather than a property of the composition. On that basis they interpreted the claim as being directed toward a composition comprised of Fab fragments of *Crotalus* venom in a pharmaceutical carrier. The Board then explained why one of ordinary skill in the art would have found it obvious to have made such a composition with the apparent rationale that one of ordinary skill in the art would have done so given that Coulter et al. taught that Fab fragments provided higher sensitivity in ELISAs. If the claim interpretation is correct then a prima facie case has been made. The Board then proceeded to address Appellant's arguments that the wherein clause represented a property of the composition not an intended use.

At page 18 of the decision of June 15, 2009 the board states:

Accordingly, faced with Appellants' arguments and Declarations, we reweigh the entire merits of the record before us on appeal. *In re Hedges*, 783 F.2d at 1039. In doing so, we seek to determine, *inter alia*, whether the composition made obvious by the combination of Sullivan and Coulter would have had the same properties as the Composition set forth in Appellants' claim 40 - e.g., the ability to treat a snakebite victim with a composition comprising Fab fragments that neutralize the lethality of the venom of a snake of the *Crotalus* genus (App. Br. 5).

*Hedges* ultimately relies on *In re Rinehart*, 189 USPQ 143 (CCPA 1976) which states at page 148:

The concept of rebuttable prima facie obviousness is well established. Cf. *In re Freeman*, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973); *In re Klosak*, 59 CCPA 862, 455 F.2d 1077, 173 USPQ 14 (1972); *In re D'Ancicco*, 58 CCPA 1057, 439 F.2d 1244, 169 USPQ 303 (1971). It is not, however, a segmented concept. When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. Though the burden of going forward to rebut the prima facie case remains with the applicant, the question of whether that burden has been successfully carried requires that the entire path to decision be retraced. An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself. Though the tribunal must begin anew, a final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached by an earlier board upon a different record.

It would appear from the Board decision that it began its consideration that the invention of claim 40 was prima facie obvious. It is equally clear from *Rinehart* that if this were the case that it would be error.

18. The Decision misapprehends the Coulter et al. article. Coulter et al. showed that Fabs raised to a single toxin "isolated from the venom of the Australian brown snake, *Psuedonaja textilis*" [Ex. 3 at p. 199, last sentence] neutralized the lethality of that single toxin. [Ex. 3 at p. 201, third full paragraph.] Coulter et al. raised Fab fragments to textilotoxin (not whole venom) and tested those Fab fragments "for their ability to neutralize the lethal effects of textilotoxin [not whole venom] in mice." [Ex. 3 at p. 201 third full paragraph.]

19. The Decision repeatedly mischaracterizes the teachings of the Coulter et al. article, confusing the distinctions between an individual toxin of a snake venom and the entire snake venom. For example, the Decision states:

Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 20, first paragraph (emphasis added).]

Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at sentence bridging pp. 20-21 (emphasis added).]

Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 21, last paragraph (emphasis added).]

Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom. [Ex. 2 at p. 23, second full paragraph (emphasis added).]

20. None of these statements is true. The Coulter et al. article taught that Fab fragments were effective in neutralizing the lethality of a single venom toxin, not an entire snake venom. Appellants were the first to teach or suggest neutralizing the lethality of an entire snake venom with an antivenom comprising Fab fragments.

It is correct that the decision appears to equate the ability of a Fab directed to a single component of a snake venom as teaching that Fab fragments are effective to neutral snake venom. Presumably, the reasoning is that given that one component of a snake venom can be neutralized by a Fab fragment that a composition comprised of Fab fragments would have similar activity. Such a conclusion is hypothetically tenable but needs to be weighed against what is known about the neutralizing activity of antivenoms. If neutralizing activity results from non-immunoglobulin proteins present in antivenom then the conclusion is not tenable. In addition, the ability to neutralize in vitro or in an animal model system must be predictive of what actually occurs in vivo i.e. subsequent to envenomation.

21. The combined teachings of the Coulter et al., article and the Sullivan et al. article would not have provided one of ordinary skill in the art with a reasonable expectation that Fabs could neutralize the lethality of:

- 1) *Psuedonaja textilis* venom as a whole by administering Fabs raised to just textilotoxin;
- 2) *Psuedonaja textilis* venom as a whole by administering Fabs raised to the entire venom; or
- 3) *Crotalus* venom as a whole by administering Fabs raised to *Crotalus* venom.

22. First, snake venoms are very complex mixtures of small and large molecules, including numerous toxins. They are so complex that most have not had all their components fully characterized, despite decades of research. Similarly, the properties of most venom components

were not known in 1984, despite decades of research. However, many of the most toxic components of snake venoms have been identified and their properties generally classified. Thus, these toxins are sometimes referred to as, for example, neurotoxins, cardiotoxins, hemorrhagics, and fibrinolytics. These properties are not necessarily exclusive, and a particular toxin may have more than one of these properties. Moreover, the individual toxins can interact synergistically with other toxins in a venom.

23. Nonetheless, most medically important venoms have been characterized in terms of the main toxic effect of their most clinically significant individual toxins, which can sometimes comprise a small percentage of a venom's total individual toxins. An antivenom must neutralize all of these clinically important toxins of a venom to neutralize the lethality of that venom. [Ex 5 at p. 83 ("An antivenom must be capable of neutralizing the injurious components of the venom."); 85 ("Thus, there may be a limited number of clinically important components that require neutralization."). Neutralizing the lethality of one toxin is not effective since other clinically important toxins could still cause lethality. [Ex. 6 at p. 319 col. 2 ("venoms are complex mixtures of proteins and other toxic factors could cause death.") ("Both the hemorrhagic and fibrinolytic activities need to be neutralized with antivenom.").]

24. *Psuedonaja textilis* was known in 1984 to have several clinically important toxins. Neutralization of the lethality of only one of those toxins, as shown in the Coulter et al. article, would not have been expected to result in neutralizing the lethality of the entire venom because the other lethal toxins would remain unneutralized. Indeed, the existing *Psuedonaja textilis* antivenom suffers from this very problem. It neutralizes the activity of textilotoxin, but it does not sufficiently neutralize the prothrombin activator, leading to coagulopathy and potentially fatal cerebral hemorrhage. [Ex. 7 at p. 80, first full paragraph. ("While CSL Ltd. antivenoms have saved many lives, persistent difficulties are being experienced with its inability to efficiently reverse the effects of the prothrombin activator. Unrelenting coagulopathy due to the slow reversal of prothrombin activator presents the added risk of cerebral hemorrhage to the victim.").] One of ordinary skill in the art would not have expected Coulter et al.'s Fab fragments to textilotoxin to have neutralized the lethality of the entire venom of *Psuedonaja textilis*. Neutralizing one weapon in the venom's arsenal of lethal toxins would not neutralize the activity of its other lethal toxins.

The examiner acknowledges that venoms are comprised of complex mixtures of polypeptides, however, the complexity *per se* does not necessitate that no conclusions can be made from studies with one venom which are applicable to another. For that reason the examiner does not find the conclusions of the following paragraph from the Dart declaration persuasive.

25. Second, one of ordinary skill in the art also would not have expected application of Coulter et al.'s Fab method to the entire venom to yield an antivenom that neutralized the lethality of *Psuedonaja textilis* venom. Given the diversity in size, charge, and structure of snake venom toxins, Coulter et al.'s ability to obtain Fab fragments that neutralized the lethality of textilotoxin would not have provided a reasonable expectation that one of ordinary skill in the art could have obtained Fab fragments that neutralized the lethality of the other clinically significant *Psuedonaja textilis* venom toxins.

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26. An Fab fragment neutralizes the lethality of a venom toxin by binding to the toxin in such a way that it blocks the binding of the toxin to its target. The Fab can itself block the binding of the toxin via steric hindrance (physically or by polarity), or the Fab can alter the structure of the toxin. In either case, the neutralization requires a specific binding between the Fab and the toxin. The Fab must have a specific 3-D structure and charge to bind the toxin so that it blocks its binding to the target. Otherwise, the Fab can bind to the toxin but have no effect on its activity. [Ex. 5 at p. 86 ("it is crucial to understand that binding of a venom component does not necessarily mean neutralization.").]

The examiner agrees with the above and additionally notes that an intact IgG could neutralize whereas its Fab or F(ab)<sub>2</sub> might not because the loss of the Fc portion resulted in loss of ability to sterically hinder binding of the venom component to its receptor.

27. The only commonality between textilotoxin and other clinically significant *Psuedonaja textilis* venom toxins is that they are contained in *Psuedonaja textilis* venom. Like all snake venoms, *Psuedonaja textilis* venom is a complex mixture of very different molecules. Coulter et al.'s teaching that Fab could neutralize the lethality of textilotoxin would have provided no more guidance on the ability of Fabs to neutralize all the other clinically significant *Psuedonaja textilis* venom toxins than it provided on the ability of Fabs to neutralize any other combination of toxins. Indeed, I am not aware of Coulter et al. ever producing a *Psuedonaja textilis* antivenom comprising Fab fragments despite the great commercial importance of *Psuedonaja textilis* antivenom to their employer, CSL Laboratories, which produced several *Psuedonaja* antivenoms.

This argument has merit in the absence of evidence that a purified F(ab)<sub>2</sub> preparation prepared from *Psuedonaja textilis* has neutralization activity.

28. Third, even if Coulter et al. did produce an antivenom that neutralized the lethality of *Psuedonaja textilis* venom, one of ordinary skill in the art would not have had a reasonable expectation of success in extrapolating results with an antivenom to *Psuedonaja textilis* venom to an antivenom to *Crotalus* venom. The snakes are in two different genera--*Psuedonaja* and *Crotalus*. Indeed they are in two different families--*Elapidae* and *Crotalidae*. There are significant differences between the venoms of those two families. The venom of elapids, while a complex mixture of chemicals, is relatively simple for snake venom. The venom of *Crotalids*, however, is extremely complex. Indeed, while *Psuedonaja* venoms can have 3-4 lethal toxins, *Crotalus* venoms have at least 6 lethal toxins. One of ordinary skill in the art would not have extrapolated antivenom results involving a single toxin of a relatively simple *Psuedonaja* venom to predict with any reasonable expectation of success what would happen with an antivenom to a much more complex *Crotalus* venom.

This returns to the complexity argument and is not persuasive.

29. Immune reactions to Wyeth's Antivenin (*Crotalidae*) Polyvalent (ACP) had long been known to be a problem. The problem was so great that some clinicians refused to give ACP, and others felt stuck between the rock of not treating a snake bite victim with an antivenom and the hard place of treating a snake bite victim with an antivenom that might be worse for the victim than the

venom being treated. The immune reactions were mainly attributed to 1) extraneous protein in the antivenom and 2) the presence of the Fc portion of the IgG molecules. The Sullivan et al. article addressed the first cause of those reactions by affinity purifying the IgG molecules that actually bound four target Crotatus venoms. [Ex. 4.] Before Applicants' invention, nobody had addressed the second aspect of this long-felt need for a safer antivenom, despite the major concern clinicians had regarding allergic reactions to ACP. I believe this is why the FDA granted CroFab orphan drug status.

Point 1) is correct and it is unclear why for other than commercial considerations no antivenoms comprised of purified IgGs had been produced. Point 2) is correct and similarly it is unclear why the antivenoms comprised of F(ab)<sub>2</sub> had not been produced. At the time of filing in 1984 the technology for purifying IgG or F(ab)<sub>2</sub> was well established.

30. Fab fragments had long been known to have potential application as an antidote, dating back at least to the use of Fabs to treat digoxin overdose in 1971. [Ex. 8 at p. 385, first paragraph.] And many antivenoms that eliminated the Fc fragment had been made and used. Those antivenoms, however, comprised F(ab)<sub>2</sub> fragments, not Fab fragments. F(ab)<sub>2</sub> fragments differ from Fab fragments by being split from the Fc portion below the hinge rather than above the hinge. The result is that F(ab)<sub>2</sub> fragments comprise two antigen binding sites, still joined at the hinge, while Fab fragments split into two separate binding sites. Despite the relatively widespread use of antivenoms comprising F(ab)<sub>2</sub> fragments, particularly in Australia, nobody prepared an antivenom comprising Fab fragments before the Applicants.

31. I believe nobody progressed to the smaller Fab fragments for two reasons. First, the F(ab)<sub>2</sub> fragment antivenoms were not as safe as had been anticipated, still resulting in allergic reaction in 30-84% of cases. [Ex. 5 at p. 90, second full paragraph.] Second, the bivalency of F(ab)<sub>2</sub> fragments allows them to bind and cross-link two toxins, often resulting in a large F(ab)<sub>2</sub>-toxin complex being precipitated out of solution; monovalent Fab fragments cannot do that. The less than expected increase in safety of F(ab)<sub>2</sub> fragment antivenoms, combined with this potential for lower effectiveness of Fab fragment antivenoms, prevented those skilled in the art from proceeding to Fab fragment antivenoms.

There is no evidence of record to indicate that any of the F(ab)<sub>2</sub> antivenoms were free of contaminating Fc portions. If they were then it would seem reasonable that they would not have had the problems inherent to the presence of the Fc chains. This lack of evidence is critical because there would be no apparent reason to proceed to make a Fab preparation given a safe and effective F(ab)<sub>2</sub>.

32. Despite those concerns, the Applicants prepared a Fab fragment antivenom and tested its ability to neutralize the lethality of Crotatus venom. Unexpectedly, they found that the Fab fragment antivenom not only neutralized the lethality of Crotalus venom, but it did so both better

than ACP and better than antivenom purified according to the Sullivan et al. article. Table 1 shows that the Fab fragment antivenom protected 6 of 9 mice from death, while ACP protected only 3 of 9. [Ex. 9 at p. 19.] Table 2 shows that the Fab fragment antivenom protected 2 of 4 mice from death, while ACP protected only 1 of 4. [Ex. 9 at p. 20.] Table 3 shows that the Fab fragment antivenom protected 4 of 4 mice from death, as did the antivenom prepared according to the Sullivan et al. article, while ACP protected only 1 of 4. [Ex. 9 at p. 20.] Table 4 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Ex. 9 at pp. 20-21.] Table 5 shows that the Fab fragment antivenom protected 5 of 5 mice from death while the antivenom prepared according to the Sullivan et al. article protected 3 of 5, and ACP protected 0 of 5. [Ex. 9 at p. 21] Finally, Table 6 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Ex. 9 at p. 22]

The results described appear to result from co-administration of antivenom or Fab with snakevenom. While the results are suggestive it is not explained how they would be predictive of venom administration followed by antibody administration.

33. Even if one of ordinary skill in the art were to read the Coulter et al. article as the Decision did—ignoring the very real and clinically important distinction between neutralizing a toxin of a venom and neutralizing the entire venom—these results are unexpected based on the Coulter et al. article. The Coulter et al. article reported that Fab had the equivalent neutralization ability as its corresponding IgG on a weight basis. [Ex. 3 at p. 202, third paragraph.] IgG has a mass of approximately 150 kDa, while Fab has a mass of approximately 50 kDa. Thus, 3 times as many Fab fragments need to be given to have the same neutralizing ability as IgG according to the Coulter et al. article. Indeed, the Coulter et al. article concludes that Fab fragments can be obtained from rabbit/gG with losses of 20-30% of initial IgG antibody activity." [Ex. 3 at p. 202, last paragraph (emphasis added).] Applicants' results surprisingly do not show such a loss in neutralizing ability for an Fab fragment antivenom. Instead, they show an increase in neutralizing ability for an Fab fragment antivenom.

This argument is unconvincing in the absence of how it compares to the results applicant obtained. It is not clear that sufficient data are presented to establish that no loss of activity is an expected result following applicant's protocol for producing Fab fragments.

34. This unexpected increase in effectiveness, combined with the increased safety, greatly interested clinicians in the field. CroFab, the commercial embodiment of the claimed invention, was first scientifically reported in the Consroe et al. article in 1995. [Ex. 10.] That article reported no adverse reactions in mice treated with CroFab. [Ex. 10 at p. 509, col. 1.] In line with the surprising results reported in the Application, it also reported that CroFab was on average 5.2 times more potent than ACP. [Ex. 10 at p. 509, col. 1.]

There is no explanation of how this evidence is supported by the disclosure of the instant application. In particular, the instant specification is silent with respect to antibodies produced in sheep or rabbits.

35. Two years later, we reported the results from the first CroFab clinical trial, demonstrating that CroFab was in fact safe and effective in a clinical setting. [Ex. 1 i.] CroFab was not approved until October 2000. After our 1997 article, I received many emails from clinicians asking when CroFab would be available, and I continued to receive that question whenever I attended professional meetings. Clinicians were clamoring to get CroFab. The consensus among the inquiring clinicians, which I shared, was that CroFab was so vastly superior to ACP in safety and in efficacy that it would completely supplant ACP in the market.

36. That is in fact what happened. CroFab could not be produced fast enough to meet the initial demand, and Wyeth announced that it was going to discontinue production of ACP within a year of CroFab's launch. [Ex. 12 at p. 32.] I recall Wyeth being vague about why they were discontinuing ACP, but those in the field viewed it as a recognition of what we all felt at the time; CroFab was so vastly superior to ACP that we all wanted to use CroFab if given a choice.

37. The essentially immediate substitution of CroFab for ACP is particularly striking in light of the significant cost premium for CroFab. CroFab was more expensive per vial than ACP, made treatment requires more vials than ACP due to its shorter half-life. Standard dosing for a moderate envenomation with ACP would cost a hospital \$3,812.50-\$6,862.60, while treatment with CroFab would cost the hospital \$10,750-\$19,350—almost 3 times as much. [Ex. 13 at pp. 225-226.] Despite that significant cost premium, clinicians pushed their hospitals to stock CroFab and stopped ordering ACP soon after the launch of CroFab.

While the success of CroFab is impressive it does not appear unpredictable given all of the clinical issues surrounding the extant treatment methods. Prior to its development it is clear from the evidence presented by declarant that there was a need for such a product.

38. For the above reasons, I believe that the Decision does not reflect how those of ordinary skill in the art would have viewed the claimed invention, nor does it reflect how those of ordinary skill in the art would have viewed the teachings of the prior art. The Sullivan et al. and Coulter et al. articles, and any other articles I know, would not have provided one of ordinary skill in the art with a reasonable expectation that an antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and a pharmaceutically acceptable carrier, would neutralize the lethality of the venom of a snake of the Crotalus genus.

Russell Declaration (Paper No. 92, May 14, 1998)  
SNAKE VENOMS

Art Unit: 1637

15. A venom is a toxic substance produced by a plant or animal in highly specialized cells or an organ and usually delivered through a biting or stinging act. Although venoms can be simple substances, as in some marine animals, in snakes they are often very complicated mixtures of individual toxins, including proteins of large and small molecular weights, phospholipases, hyaluronidase, collagenase, acidocollagenase, L-amino acid oxidase, hydrolases, nucleotidases, lipids, metalloproteins, free amino acids, steroids, aminopolysaccharides, amines, quinones, 5-hydroxytryptophan, and other substances. For example, snake venoms of the family Crotalidae comprise at least 20 different compounds. In some Crotalus sp. snake venoms, there may be 100 different protein fractions, 25 of which may be enzymes. Due to their complexity, the full composition of snake venoms is unknown.

16. Not only is the full composition of snake venoms unknown, but the pharmacological effects of some constituent toxins are unknown. Although the individual components of some snake venoms are known to have pharmacologic activities, including hematologic, cardiotoxic, neurotoxic, and other properties, each component may have more than one of these activities, and components may have different actions on different cell types. Furthermore, some of the more important reactions in humans to Crotalus envenomation are autopharmacologic or the result of synergisms between different venom components. As a result, of the at least 100 known components of Crotalus snake venoms, less than 20 compounds have known pharmacologic activities. Russell, F.E. (1980) Snake Venom Poisoning at p. 139 (attached as Exhibit 2).

17. Indeed, it would have been clear to a researcher in the field that we used the term "venom" in the subject patent application to mean a venom comprising several different toxins, not just a single toxin. Each venom discussed in the application contains several toxins. Furthermore, the application specifically discusses isolating specific venom proteins (toxins) from the snake venom. Specification at 6, last sentence. Accordingly, a researcher in the field would have understood from the subject patent application that we used the term "venom" in the subject patent application to mean a mixture of toxins, not a single toxin isolated from a venom.

18. The term "antivenin" was first used to identify the first antiserum for snake venom poisoning, and we specifically defined "antivenin" in the specification in this way: Antivenin is a suspension of venom-neutralizing antibodies, prepared from the serum of animals (typically horses), hyperimmunized against a specific venom or venoms. See Specification at 4, lines 19-22. Although the terms "antivenin" and "antivenom" are often interchanged, researchers in the field now use the term "antivenom" because the World Health Organization ("WHO") has decided that "antivenom" is the preferred term. WHO/B5/80-1292 BLG/VEN/80.1 Rev. 1 (attached as Exhibit 3). Indeed, although I was one of the dissenters in the WHO vote and prefer the term "antivenin," I have previously indicated that the terms "antivenin" and "antivenom" are now interchangeable: "ANTIVENIN (ANTIVENENE, ANAVENIN, ANTIVENIMEUX, ANTIVENINIUM, ANTIVENOM)" Russell, F.E. (1988) Snake Venom Immunology: Historical and Practical Considerations. J. Toxicol.-Toxin Rev. 7(1), 1 (attached as Exhibit 4).

19. At the time of the application, the only commercially available antivenom for envenomation by North American snakes of the family Crotalidae was Antivenin (Crotalidae) Polyvalent (equine origin) (Wyeth Laboratories, Philadelphia, PA). Since this was the only commercially available antiserum for snakes in the United States, it was sometimes referred to as simply "antivenin." However, it would have been clear to a researcher in the field that our recitation of "antivenin" in the specification referred generically to all antivenins, not specifically to Wyeth's Antivenin (Crotalidae) Polyvalent (equine origin) because, among other reasons, we specifically referred to Wyeth's product as "ACP" in the application. e.g., specification at 2, line 11. Furthermore, we compared Wyeth's product to our claimed antivenom in the specification at page 23, lines 5-15.

Prior Treatment of Crotalidae Envenomation

20. Approximately 8,000 people are bitten by venomous snakes in the United States each year. Most of these people are bitten by *Crotalus*, a genus of the family Crotalidae. Before the advent of pharmacological methods of treating snake envenomation, it is estimated that envenomation by *Crotalus* resulted in approximately 7% mortality.

21. The most effective and most common treatment of Crotalidae envenomation is the administration of antivenom. The first reported use of a snake antivenom in humans occurred in the late 19th century. The only commercially available antivenom for North American Crotalidae is ACP, which first became available in 1947. Soon after the development of the first antivenoms, doctors recognized that they could elicit serum sickness, an allergic reaction to the antisera that was sometimes more deleterious than the venom. Over 75% of patients treated with ACP develop some manifestation of serum sickness. The problem of serum sickness can be so great that physicians may not administer antivenom for some cases of envenomation. Indeed, ACP can only be obtained in a kit that also contains test serum for possibly detecting serum sickness before administering the antivenom.

22. The serious deficit of serum sickness with antivenom has long contributed to extensive research on modifying existing antivenoms or developing new antisera. Since the serum sickness results from immune reactions of the patient to the immunoglobulin component of the antivenom, which actually binds to the venom toxins, much of this research focused on using fragments of immunoglobulin molecules that might not provoke a immune reaction.

23. As the figure attached as Exhibit 5 shows, a molecule of immunoglobulin comprises two heavy chains and two light chains with the heavy chains linked by two disulfide bonds at their hinge region. Each light chain forms an antigen binding site with the corresponding heavy chain at the end distant to the hinge region.

24. Cleavage of immunoglobulin with pepsin cleaves the IgG molecule below the disulfide bonds, resulting in a single Fc fragment and a single F(ab)<sub>2</sub> fragment (sometimes called an F(ab')<sub>2</sub> fragment), which contains the two antigen binding sites. In contrast, cleavage of IgG with papain cleaves the immunoglobulin molecule above the disulfide bonds, resulting in a single, larger Fc molecule and two Fab fragments (sometimes called F(ab) fragments), each containing a single antigen binding site. Specification at 2, lines 25-43.

25. In the 1960s, researchers began experimenting with antivenoms, comprising F(ab)<sub>2</sub> fragments. These became commercially available outside the U.S. in 1969. Although these F(ab)<sub>2</sub> antivenoms produced less serum sickness, as would be expected from their greater purity, such antivenoms appeared to some to be less effective than antivenoms comprising whole immunoglobulin. Consequently, Crotalidae antivenoms comprising F(ab)<sub>2</sub> fragments were not produced in the United States.

#### Antivenoms Comprising Fab Fragments Were Expected to Fail

26. As of 1984, no significant improvements in antivenoms had been made since antivenoms comprising F(ab)<sub>2</sub> fragments became available in 1969. Significantly, although serum sickness had long been recognized as a major problem with antivenoms, and although smaller antibody fragments had long been known to be less immunogenic, no researcher developed an antivenom comprising the smaller Fab fragments. The development of antivenoms comprising antibody fragments stopped at the larger F(ab)<sub>2</sub> fragments because researchers in the field expected that Fab fragments would be less effective than F(ab)<sub>2</sub> fragments. Indeed, those researchers believed that Fab fragments might actually alter the toxicity of a Crotalidae venom.

While this may well be true it is unclear that the actual size of the market influenced the commercial manufacturers.

27. Researchers in the field were concerned that antivenoms comprising Fab fragments would be less effective than antivenoms comprising  $F(ab)_2$  fragments. because: 1) the Fab fragments would not prevent the various venom toxins from binding to their site of action as well as the  $F(ab)_2$  fragments; 2) the Fab fragments would not precipitate the various venom toxins; and 3) the Fab fragments would not neutralize sufficient venom toxin before being cleared because of their short half-life.

28. Immunoglobulins neutralize toxins in several ways. For example, they bind specifically to epitopes present on the toxins. In the case of a polyclonal antivenom, this may involve several epitopes present on more than one antigen. These antigen-antibody complexes are readily eliminated by the reticuloendothelial system, or by other mechanisms.

29. Since  $F(ab)_2$  fragments contain two antigen binding sites, like whole immunoglobulin, it was suspected that they could more effectively bind to repeating antigenic determinants on large proteins than could Fab with only one binding site. Sell, S. (1987) Basic Immunology: Immune Mechanisms in Health and Disease at p. 89, Fig. 6-3 (attached as Exhibit 6). As a result, it was felt that while Fab fragments might bind to venom toxins, they would not be as effective as whole IgG or  $F(ab)_2$  fragments.

Where is there any evidence that either larger proteins or the components of snake venom contain repeating determinants?

30. Furthermore, researchers in the field expected that antivenoms comprising Fab fragments would not be as effective as antivenoms comprising  $F(ab)_2$  fragments because Fab fragments have a shorter half-life than  $F(ab)_2$  fragments in vivo. Venom components are usually injected into subcutaneous tissues. Since many of the venom toxins are large, hydrophobic molecules, they are slowly released from these injection areas. This results in the "venom depot effect" where toxins are continuously released into the systemic circulation long after the initial bite.

However, the smaller Fab fragments should exhibit more rapid tissue infiltration, and ameliorate the local effects of the venom. This raises the interesting question of whether or not an anti-venom comprised of either IgGs or  $F(ab)_2$  in combination with Fabs would be more effective than either IgG or  $F(ab)_2$  alone.

31. The molecular weight of an Fab fragment is in the range of 45-55 kd. As can be seen from Exhibit 5, the molecular weight of an  $F(ab)_2$  fragment is over twice the molecular weight of an Fab

fragment and approximately the same molecular weight as a whole IgG. As a result of these differences in molecular weights, Fab fragments are eliminated more quickly than  $F(ab)_2$  fragments and whole IgG. Unbound Fab fragments are small enough to be removed by the renal system. Consequently they have a half-life of about 17 hours. Indeed, Fab fragments are completely eliminated in only 24 to 26 hours.

32. In contrast,  $F(ab)_2$  fragments and whole IgG are too large to be eliminated by the renal system. Consequently they have a longer half-life, approximately 50 hours. The shorter half-life of Fab fragments compared to the half-life of venom, and compared to the half-life of  $F(ab)_2$  fragments, led researchers in the field to expect that antivenins comprising Fab fragments would not be effective against Crotalidae envenomation.

33. Not only did researchers in toxinology and pharmacology believe that antivenoms comprising Fab fragments would be less effective than antivenoms comprising  $F(ab)_2$  fragments, they suggested that antivenoms comprising Fab fragments might actually be harmful. They expected that the Fab fragments that did not bind venom toxins during their short half-lives might not only fail to precipitate the venom toxins, but could actually redistribute the venom toxins to organs where the toxins might concentrate.

34. The binding of whole IgG,  $F(ab)_2$  fragments, and Fab fragments to venom toxins is a dynamic process; even at a state of equilibrium, individual venom toxins are constantly being bound and released. The 45-55 kD molecular weight of an Fab fragment is close to the upper filtration limit of the kidney. As stated, Fab can be cleared by the renal system, but the higher molecular weight  $F(ab)_2$  fragments and whole IgG cannot. Whole IgG and  $F(ab)_2$  fragments are instead cleared by the reticuloendothelial system and the liver, as are any unbound venom toxins.

35. In addition to allowing Fab fragments to be eliminated by the renal system, resulting in a shorter half-life, the small size of Fab fragments, as compared to  $F(ab)_2$  fragments, also allows Fab fragments to be distributed to more parts of the body. Researchers in the field were concerned that this rapid clearance and larger volume of distribution of Fab fragments compared to  $F(ab)_2$  fragments would result in a more systemic toxicity than a localized one.

36. Researchers in the field also speculated that the larger volume of distribution of the Fab fragments would allow Fab fragments to bind the venom toxins earlier than  $F(ab)_2$  fragments. In addition, Fab fragments might bind venom toxins that  $F(ab)_2$  fragments could not reach. As the bound Fab-toxin complex circulated throughout the body, however, Fab fragments could periodically release these toxins in their state of equilibrium. The unbound Fab fragments would be rapidly eliminated by the renal system, which could not eliminate the larger Fab-toxin complexes. Researchers, therefore, were concerned that such venom toxins would be redistributed to other areas of the body, perhaps concentrating in areas of high blood flow, especially, the kidneys, heart, nervous system, and lungs. Thus, venom toxins that would have been released slowly from the bite site due to the venom depot effect would be redistributed to these areas of high blood flow. In other words, the Fab fragments would effectively serve as a vehicle, redistributing and concentrating these venom toxins from subcutaneous muscles and fat to the kidneys, heart, nervous system, and lungs, which would not have otherwise received a relatively high concentration of these toxins.

It is not at all clear that Fabs would lead to higher concentrations in other tissues relative to that occurring during normal venom redistribution in the body.

37. This concern was not merely a theoretical concern, as was later demonstrated by Faulstich et al. Faulstich et al. (1988) Strongly Enhanced Toxicity of the Mushroom Toxin  $\alpha$ -Amanitin by an Amatoxin-Specific Fab or Monoclonal Antibody. Toxicon 26, 491 (copy attached as Exhibit 7). Faulstich et al. conducted a series of studies attempting to treat  $\alpha$ -amatoxin poisoning with Fab fragments. Alpha-amatoxin is a high molecular weight toxin that is similar to some snake venom toxins. As a high molecular weight toxin,  $\alpha$ -amatoxin cannot be cleared by the renal system. Rather, like many snake toxins, it is cleared by the liver. Since  $\alpha$ -amatoxin is concentrated in the liver after oral ingestion, it is primarily toxic to liver cells.

38. Faulstich et al. discovered that the Fab fragments did not decrease the toxicity of  $\alpha$ -amatoxin in mice, but rather increased the toxicity of  $\alpha$ -amatoxin by a factor of 50. Id. at 497. Furthermore, the Fab fragments resulted in  $\alpha$ -amatoxin being specifically toxic to kidney cells rather than liver cells. This is exactly what one of ordinary skill in the art would have predicted. The Fab fragments bound the high molecular weight  $\alpha$ -amatoxin, and then unbound it in their state of equilibrium at sites of high blood flow. This unbinding at sites of high blood flow, especially the kidneys, resulted in the  $\alpha$ -amatoxin being concentrated in these tissues.

39. Similarly, Balthazar et al. conducted research on Fab fragments against digoxin. Balthazar et al. (1994) Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug. J. Pharm. Exp. Ther. 268, 734 (attached as Exhibit 8). Digoxin is unlike most Crotalidae venom toxins; it is a very small molecule. Digoxin is small enough that the renal system can clear the Fab-digoxin complex. Since the renal system can filter the Fab-digoxin complex, the Fab did not redistribute and concentrate digoxin, as one of ordinary skill in the art would have predicted. Accordingly, Balthazar et al. found that F(ab) fragments effectively treated digoxin toxicity.

40. However, Balthazar et al. recognized the potential problems of Fab therapy for large toxins, like  $\alpha$ -amatoxin and some Crotalidae venom toxins: |

First, the alteration of drug distribution which accompanies antibody drug complexation may result in a potentiation of drug toxicities or the development of **new drug toxicities in certain cases .... The risk of redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach.

Id. at p. 738, paragraph bridging cols. 1 and 2 (emphasis added).

$\alpha$ -amatoxin is not a high molecular weight toxin, see the attached Wikipedia page. In addition, intact IgG was also found to increase the toxicity of  $\alpha$ -amanitin. Faulstich et al. also note that the drug's behavior is altered when conjugated to carrier proteins with a concomitant increase in toxicity. Their results do support the concept that complexation of a drug with a carrier may result in changes in tissue specificity. But, this would be a known concern in developing any treatment. Clearly, there are drugs for which antibody therapy is effective as evidenced by the Balthazar et al. study.

41. Accordingly, researchers in the field were concerned that treatment with an antivenom comprising Fab fragments would be a harmful treatment for high molecular weight toxins, not an advisable treatment, because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities and converting a localized toxicity into a systemic toxicity. Faulstich et al. confirmed this concern with a toxin that is of a similar molecular weight as many snake venom toxins.

This conclusion is not tenable because the molecular size of  $\alpha$ -amanitin is considerably smaller than an average polypeptide. Indeed, given that Faulstich et al. teach that intact IgG exhibits the same effect one would have been lead to the conclusion that antibodies directed to small molecular weight components in snake venom would lead to increases in toxicity. Following declarant's line of reasoning this would have been a deterrent to developing an anti-venom.

42. Balthazar et al. reinforced this concern by showing that this effect did not occur with a low molecular weight toxin that the renal system could clear as part of an Fab-toxin complex. Indeed, despite the effectiveness of their treatment, Balthazar et al. specifically discussed their concern that Fab fragments might alter drug toxicities or redistribute systemic toxicities.

43. In sum, prior to our invention, researchers in the field did not have a reasonable expectation of success that an antivenom comprising Fab fragments to Crotalidae venom would be effective. Despite known problems with the only, commercially available antisera for Crotalidae envenomation and much research since 1947, no researcher had developed an antivenom comprising Fab fragments. Furthermore, although F(ab)<sub>2</sub> fragments had been used in antivenoms since the late 1960s, those of ordinary skill in the art had not progressed beyond F(ab)<sub>2</sub> fragments to the smaller Fab fragments.

44. Even though Fab fragments were known to be highly effective in reducing the serum sickness, researchers in the field did not create a Crotalidae antiserum comprising Fab fragments because they were sure such a product would not work. Researchers in the field were concerned that such an antivenom would be ineffective because: 1) the Fab fragments could not sterically hinder the Crotalidae venom toxins from binding to their target; 2) the Fab fragments could not precipitate the venom toxins; and 3) the Fab fragments had too short a half-life in vivo to be able to bind some to snake venom toxins. Furthermore, researchers in the field were concerned that such an antivenom might actually increase the toxicity of the venom by redistributing the more deleterious toxins.

No evidence has been presented to support 1) nor 2) that precipitation is crucial to neutralization-it might well be a mechanism for enhanced toxicity at the site of envenomation resulting from precipitation in the tissue thereby enhancing the depot effect of the toxin nor 3) that half-life relates to binding ability.

The Coulter et al. Reference

45. I understand that the Examiner has rejected the pending claims in Paper No. 29 over numerous references, including the Coulter et al. reference (Coulter et al. (1983) Simplified Preparation of Rabbit Fab Fragments. J. Immun. Meth. 59, 199 (attached as Exhibit 9)). For the above reasons, none of the references the Examiner has cited, alone or in combination, teach or suggest an antivenom comprising Fab fragments against a Crotalidae venom with a reasonable expectation of success.

46. However, the Coulter et al. reference merits individual mention in order to clarify the Examiner's understanding of it. Coulter et al. used textilotoxin, "a neurotoxin" and the primary toxin in the venom of the Australian brown snake (*Pseudonaja textilis*). *Id.* at 199, last sentence. The pending claims recite a snake of the genus *Crotalus*, a *ii* genus of the family Crotalidae. As can be seen from its name, the snake Coulter et al. used is not a member of the genus *Crotalus*, nor even of the family Crotalidae. Rather, it is a member of the genus *Pseudonaja*. Indeed, O'Doul's Toxicology teaches that Coulter et al.'s snake is an elapid, Russell (1996) Toxic Effects of Animal Toxins. In Casarett and Doull's Toxicology: The Basic Science of Poisons, (5th Ed.) at *ii* p. 802 (attached as Exhibit 10), and the elapids are of the family Elapidae, not Crotalidae. Snake Venom Poisoning at p. 5.

47. Furthermore, textilotoxin is simply a single toxin from Australian brown snake venom. As I discussed above, the terms "antivenom" and "antivenin" mean an immunotherapy mixture against a snake venom, not simply a single snake toxin. As I have also noted, snake venoms are complex mixtures of many substances, including many different toxins. Snake venoms, particularly those of snakes of the family Crotalidae, are composed of many different toxins. Each of the individual toxins can act synergistically *in vivo* and may also induce autopharmacologic reactions. Indeed, basic toxicology texts caution against extrapolating results from individual venom toxins to whole venoms. Toxic Effects of Animal Toxins at p. 802; Snake Venom Poisoning at p. 168. Accordingly, one would not have expected Coulter et al.'s results with Fab to a single toxin to predict similar results with Fab to a Crotalidae snake venom, including a *Crotalus* snake venom.

48. Most importantly, Coulter et al. did not treat envenomation with their Fab fragments. Rather, Coulter et al. first mixed textilotoxin with their Fab fragments *in vitro*. Coulter et al. at p. 901, 3rd full paragraph. Coulter et al. then injected the already bound Fab-textilotoxin complex intravenously. This treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one would have expected. Since the Fab-textilotoxin mixture was injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts. Accordingly, the Coulter et al. reference would not have provided a reasonable expectation of success for an antivenom comprising Fab fragments to any venom toxins.

It is unclear how declarant can conclude that the results with Fab fragments were expected given his previous arguments regarding the expected behavior of Fab fragments in paragraph 34. The result is surprising in that the Fab lacks the Fc chain which is critical to internalization via the Fc receptors present on cells of the reticuloendothelial system. In addition, co-administration should have enhanced

tissue redistribution because the Fab would have already had its component bound rather than having to migrate to the site of envenomation, bind the toxin and then relocate. The more interesting issue is the artificiality of the experiment compared to the reality following envenomation. There is good reason to question whether the dynamics of venom clearance is reasonably modeled by experiments wherein the components are injected simultaneously. If one of ordinary skill in the art did not consider the Coulter et al. experiment predictive of what would normally occur then declarant's conclusion is reasonable. But, this also raises the question of whether simultaneous administration intraperitoneally is a reasonable model.

49. Similarly the observation of Coulter et al. that enzyme-linked immunoabsorbent assays with higher sensitivity had been claimed when Fab is used instead of whole IgG would not have suggested combining any of the cited references with a reasonable expectation of success. As in the case of Coulter et al.'s actual results, in vitro observation would have been irrelevant to the lack of expectation of success in vivo since the reasons one would not have had a reasonable expectation of success were due to the expected in vivo action of the Fab fragments.

50. Indeed, Sorkine et al. conducted a similar experiment in 1983 by mixing Fab fragments with a venom of a non-Crotalidae snake prior to injection into a mouse, and they obtained similar results. Sorkine et al. (1995) Comparison of F(ab')<sub>2</sub> and Fab Efficiency on Plasma Extravasation Induced Viper aspis Venom. Toxicon 33,257 (attached as Exhibit 11). This treatment resulted in a considerable reduction in capillary permeability. However, the Fab fragments were much less effective when they were administered in vivo separately from the venom. As Sorkine et al. state "these data showed firstly that the in vitro neutralization of the venom by immunoglobulin fragments does not reflect their in vivo efficiency." Id. Thus, the Sorkine et al. reference shows that one would not have expected Coulter et al.'s in vitro neutralization results to predict the effectiveness of antivenoms comprising Fab fragments in vivo.

Sorkine et al. appears to have been published in 1995 and suggests that the co-administration of Fab and venom represents an artificial system not predictive of what occurs in vivo. It is not clear how it should be viewed in light of Sullivan (1987) discussed above. It is confirmatory of the remarks made concerning paragraph 48 above.

51. In 1984, no clinician or researcher expected that a Crotalidae snake antivenom comprising Fab fragments would be effective in treating Crotalidae snake envenomation. Thirty-seven years of research primarily aimed at reducing the serum sickness produced by ACP and fifteen years of research since the first, disappointing F(ab)<sub>2</sub> antivenom had convinced those of ordinary skill in the art that a Crotalidae antivenom comprising Fab fragments would be less effective than the known antivenoms. Furthermore, those of ordinary skill in the art actually expected a Crotalidae antivenom comprising Fab fragments to increase the lethality of the snake venom. Accordingly, there was no expectation of success in using any Crotalidae antivenom comprising Fab fragments to treat Crotalidae envenomation, let alone an expectation of success in using a Crotalus antivenom comprising Fab fragments to treat Crotalus envenomation.

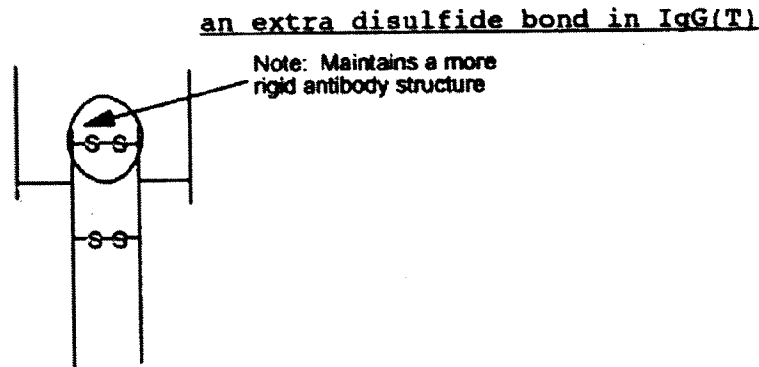
To the extent that an antivenom comprising Fab fragments means an antivenom with no F(ab)<sub>2</sub> or IgG the examiner agrees.

Sullivan Declaration (Paper No. 124, November 21, 1995)

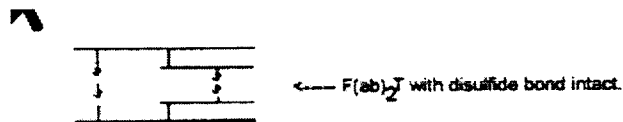
5. Those of skill in the art did not expect F(ab) fragments to venom to be useful as antivenins. The development of antivenin production through the years stopped at a final product of F(ab)<sub>2</sub>'s. For several reasons, it was not obvious that smaller fragments would be clinically efficacious; these reasons are summarized here and discussed more fully below. (a) F(ab) is cleared more quickly than F(ab)<sub>2</sub>, antivenin or IgG. Slower clearance of large molecular weight venom proteins was known to be a fact. In humans, venom proteins have a prolonged half life (T<sub>1/2</sub>) with slow elimination from the body. An F(ab) fragment would be predicted to be totally eliminated within 5 half-lives or 24-26 hours, whereas venom protein requires weeks for elimination. An F(ab) fragment would not increase renal elimination of venom protein since the combined molecular weight of F(ab): protein is greater than the 45,000-50,000 M.W. filtration limit of the kidney. The reticuloendothelial system (RES) and liver are the main organs that eventually clear venom proteins, IgG, and F(ab)<sub>2</sub>. (b) Whole IgG and F(ab)<sub>2</sub> would "stay around" longer with venom, rendering the proteins essentially nontoxic, or bound up by antibody, until cleared by the RES and liver. The F(ab), with shorter T<sub>1/2</sub> and increased renal clearance, would not be available to bind venom. Thus, one would reason, as did the experts at the time, that the use of F(ab) would be relatively or absolutely contraindicated because toxicity might be prolonged and toxin, if redistributed, would be more harmful at other sites in the organism to which a short T<sub>1/2</sub> F(ab) would "taxi" and deposit the toxin, leaving it.

This line of reasoning is persuasive to the extent that the antivenom would consist of only Fabs.

6. The early success of equine-derived antivenin containing IgG(T) antibody was due to the nature of the IgG(T) antibody, which has an extra disulfide bond.



The extra disulfide bond allows IgG(T) to bind with enhancement to repeating protein antigens. An  $F(ab)_2$  of IgG(T) would do the same. An  $F(ab)$  would not, thus diminishing clinical efficacy. The nature of the equine IgG(T) has been known for years. This could be obviously reasoned, thus an  $F(ab)$  would not be thought to be of clinical value in negating poisoning from venoms.



My early work with horse antiserum produced an  $F(ab)_2T$  fragment. It was obvious that the  $F(ab)_2T$  would bind "better" than  $F(ab)$  because of considerations discussed above.

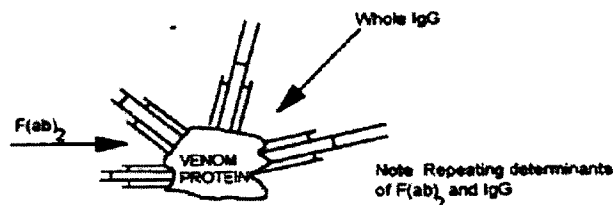
This is not persuasive regarding the basis for the effectiveness of IgG(T) as no evidence has been presented that its effectiveness in neutralizing venom results from its ability to bind repeating determinants. IgG(T) has been shown to precipitate conventional polypeptides and its reaction with repeating determinants is at the very least complicated. The spatial arrangement of the determinants is apparently more critical than their mere repetition. See McGuire et al. (1979) which also discloses that IgG(T) does not activate the phagocytic pathway.

7. The molecular weight of  $F(ab)$  is about 45,000 daltons. It has a half life that is less than that of  $F(ab)_2$ .  $F(ab)_2$  has a half life similar to that of IgG. The Vd (volume of distribution) of  $F(ab)$  is greater than that of  $F(ab)_2$ , which in turn is greater than that of IgG. The rapid renal clearance and enhanced elimination of  $F(ab)$  was expected to be a detriment to treating clinical envenomations. Thus, thought concerning the art and science of antibody fragments did not indicate the obviousness of  $F(ab)$  fragment clinical efficacy. In fact, it

was the opposite. In the early 1980's I and others maintained and discussed our concerns that F(ab) would redistribute toxic venom proteins throughout the body, thus producing venom pathology at tissue sites and organ systems not typically seen in patients treated. Due to higher Vd and more rapid clearance, the F(ab) was predicted to potentially redistribute and concentrate venom proteins in other organ systems: kidneys, heart, central nervous system, peripheral nervous system, liver, lung and other blood flow areas. The F(ab) would "leave" venom at these new tissue sites, "depositing" the poison where it was not previously found. Instead of swelling and local necrosis, there might be coagulopathy, direct cardiotoxicity, liver and kidney damage, potential central nervous system, and peripheral nervous system damage. This could be predicted, and is the reason why others stopped at the F(ab)<sub>2</sub> phase. Thus, investigators went no further than F(ab)<sub>2</sub> for venom or protein poisoning.

8. Protein (venom) toxicity is reduced by binding of antibody to repeating protein determinants and sterically hindering venom binding to tissue sites. F(ab)<sub>2</sub> and IgG have similar ability to preserve the important repetitive binding to determinants. F(ab)'s ability is predicted to be diminished due to their physical nature.

Steric hindrance enhancement by F(ab) and IgG.



No experimental evidence supporting this hypothesis has been presented.

No evidence has been presented that snake venom proteins have repeating determinants nor that Fabs would necessarily not sterically hinder binding of a venom polypeptide to its target.

9. Digoxin and other drugs (non-proteins) have small molecular weights and vary in their clinical pharmacokinetic parameters (T<sub>1/2</sub>s, V<sub>ds</sub>, K<sub>12</sub>, K<sub>21</sub>). (K<sub>12</sub> refers to the rate of distribution of drug to peripheral tissues, where the drug acts on receptors. K<sub>21</sub> refers to the rate of redistribution from peripheral tissues back to a central compartment, from where the drug is eliminated.) Clinical pharmacokinetic parameters of drugs vary greatly and determine toxicity and clinical pharmacology. Pharmacodynamics also vary greatly among drugs. Anti-digoxin F(ab) is efficacious in digoxin overdose as it would have been predicted to be given the knowledge of digoxin and F(ab)s. There are examples of F(ab) failure in treating other cases of toxicity. Anti-tricyclic Fab did not work in experimental drug overdose with tricyclic antidepressants. Anti- $\alpha$ -amatoxin Fab increases toxicity. I and others questioned whether anti-venom F(ab)'s would be effective antivenins. The answer could not be known until experiments and clinical trials were performed.

This suggests that the interaction of Fabs is dependant on the system in which they are in and that this behavior is not predictable.

10. There are differences between the tissue targets of the toxins discussed above:
- Digoxin has one main target: cardiac tissue.
  - Tricyclic antidepressants have several targets, including cardiac tissue and multiple central nervous system sites
  - Tricyclics also have multiple tissue binding sites.
  - Venom has several target tissues.
  - $\alpha$ -Amatoxin has several target sites consisting of any cells' nucleus.

F(ab) to digoxin works; Fab to  $\alpha$ -amatoxin fails; F(ab) to tricyclic failed in an animal model. Therefore, those of skill in this art predicted that an F(ab) to venom would fail, with the result of increased toxicity due to very little therapeutic efficacy or redistribution of toxin.

This conclusion is untenable because some Fabs work and some do not and there is nothing to suggest that results from small molecule studies are predictive of the results with proteins.

11. To summarize, the failure of F(ab) antivenins was predicted for the following reasons:
- F(ab) would cause redistribution of protein toxins to distant, nontargeted sites.
  - F(ab) would act as a "taxi" and deposit venom poisons at various organs as it quickly left the body via the kidneys.
  - F(ab)'s had failed with other drugs and protein poisons that, like venom, have multiple targets (tricyclics,  $\alpha$ - amatoxin), in part because redistribution increased toxicity.

Venom proteins redistribute as they leave the depot. No evidence suggests that Fabs facilitate such redistribution.

12. Surprisingly, our results were the opposite from what was predicted:
- F(ab) unexpectedly decreased mortality in early animal studies.
  - Clinical studies show that the efficacy of Fab is equal to or greater than F(ab)2 or IgG.
  - The effect of F(ab) on decreasing edema was superior to that of F(ab)2.

It is not clear that one would predict failure based on the results with other systems. It seems more reasonable that one could not predict the behavior at all.

13. For the foregoing reasons, I, as a qualified expert in the areas of F(ab) antitoxins and treatment of envenomation, believe that it was not obvious to use anti-venin F(ab) to treat snake envenomation. In fact, those of skill in the art expected that F(ab) treatment would fail or increase toxicity of the venom. Such treatment would therefore have been medically unsound and contraindicated.

Smith Declaration (Paper No. 132, May 24, 1995)

7. Antivenins comprising intact antibodies have been sold commercially since at least 1947. Antivenins comprising F(ab)<sub>2</sub> fragments have been sold commercially since at least 1969. No significant improvements have been made to commercial antivenins since 1969.

It is noted that no evidence regarding the sources of and composition of the antivenoms is described.

8. Digoxin is a small molecule that is ingested and dispersed in the bloodstream and interstitial fluid. Snake venoms are large hydrophobic molecules that are injected into the muscle or fatty tissues and slowly released from the site of the bite. Because F(ab) is cleared rapidly, one might have expected that a single administration of F(ab) antivenin would not effectively neutralize later-released venom.

This aspect appears to be known and it would seem obvious that it would be overcome by repeated injections of F(ab). However, the clinical implications of such repeated injections would clearly influence the issue. They would have to be balanced against the known clinical issues surrounding the administration of the extant antivenoms.

9. F(ab)<sub>2</sub> fragments and intact antibodies have two binding sites, whereas F(ab) fragments have only a single intact antibodies or initiate complement fixation like such complexes. Formation of such complexes is important to their removal by the reticuloendothelial system, where large complexes are cleared most quickly.

10. Because F(ab) fragments are relatively small (compared to intact immunoglobulins and F(ab)<sub>2</sub> fragments) and venom molecules are relatively large (compared to digoxin), one skilled in the art would have been concerned that a F(ab)-venom complex would retain toxicity.

There is no explanation why size alone would result in retention of toxicity.

11. Paragraphs 12 and 13 describe a clinical study in which patients have been treated with TAB001, a purified ovine F(ab) fragment for treating Vipera berus envenoming, and compared to patients treated with a conventional F(ab)<sub>2</sub> antivenin.

12. Methods A multicenter study was set up in Sweden in 1991 to assess the efficacy and safety of TAB001, a venom-specific affinity purified antivenom, in patients with moderate-severe Vipera berus envenoming. The criteria for inclusion in the trial were: (i) circulatory failure responding poorly to symptomatic treatment or recurring; (ii) protracted or recurrent gastrointestinal symptoms; or (iii) less severe circulatory disturbances or rapidly progressing local edema with

any of the following – pronounced leucocytosis; extensive hemolysis, coagulopathy; metabolic acidosis; increased serum activity of monitored according to a protocol describing clinical and laboratory procedures to be followed throughout their inpatient stay and at follow-up on three occasions during the month after discharge. Two earlier reported patient groups with a similar degree of envenoming were used as control groups for evaluation of treatment efficacy. In one of these groups, consisting of sixteen patients, no antivenom was given, whereas in the other group, including thirty patients, an equine F(ab)<sub>2</sub> antivenom was used in a dose of 1.4 g. The first four patients received 100 mg of TAb001 administered via i.v. infusion over 30 minutes. The dose was then increased to 200 mg to determine if a higher dose could further reduce the incidence of progressive swelling associated with Vipera berus bites.

### 13. Results

The Results are presented in the following Table:

| Parameter   | Type of Antivenom Treatment            |  |                   |
|---|--|--|-------------------|
|   | No Antivenom<br>(n = 16) <sup>1/</sup> | Conventional<br>(n = 30) <sup>2/</sup> | TA001<br>(n = 18) |
| Average Hospital<br>Median Stay (Days)                  | 6                                      | 3                                      | 3                 |
| Extensive Edema<br>Involving Trunk                      | 88%                                    | 23%                                    | 17%               |
| Pronounced Anemia<br>(>10% below normal<br>lower limit) | 44%                                    | 10%                                    | 17%               |
| Associated Allergic<br>Side Effects                     | \                                      | 10%                                    | None              |

Previous experience<sup>1/2/</sup> suggests that the most suitable parameters for evaluating the outcome of antivenom treatment are the development of edema, anemia and the duration of hospital stay. These features were studied in patients treated with TAb001 and compared with the corresponding parameters in patients treated with either conventional antivenoms or no antivenom. TAb001 appears to be equally effective as the conventional antivenom in reducing the occurrence of extensive edema and severe anemia as well as shortening hospital stay. Moreover, to date, no allergic events, suggesting an immediate or delayed hypersensitivity response, have been observed after administration of TAb001, whereas 10% of those given conventional antivenom had allergic side-effects.

1/ Persson, H., and Irestedt, B., "A study of 136 cases of adder bite treated in Swedish hospitals during one year," Acta Med. LScand., 210: 433-9 (1981).

2/Karlson-Stiber, C., and Persson, H., "Antivenom treatment in 8D-NER, L.L.P. 30 cases of Vipera berus envenomation in Sweden 1985-1989," Br Med. J. Submitted for publication.

The results are suggestive of the efficacy of ovine Fabs. However, the instant specification makes no mention of employing ovine Fabs nor is it clear that

results with equine F(ab)<sub>2</sub> can be compared to those with ovine F(ab) especially in view of Sullivan's remarks (see Sullivan Declaration at ¶¶ 6 & 8).

*Consideration of Obviousness*

One of ordinary skill in the art would have come to Sullivan with knowledge of the history of antivenom development and treatment. Said person would have been well aware of the purity of the various antivenoms and the potential clinical complications resulting from its administration. In reading Sullivan one of ordinary skill in the art would have recognized that the effectiveness of purified IgG in neutralizing venom indicated that they were sufficient for neutralizing activity. In addition, one of ordinary skill in the art would have proceeded to prepare F(ab)<sub>2</sub> fragments as a potential antivenom. Antivenoms containing impure F(ab)<sub>2</sub> fragments appear to have been commercially available and their effectiveness suggests that the activity did not require intact IgG which suggests that the Fc chain does not mediate neutralization activity.

The examiner has not been able to obtain product information regarding the F(ab)<sub>2</sub> antivenoms available at the time the invention was made to establish their purity nor has a search of the scientific literature provided any information in this regard.

The results presented by Coulter et al. are suggestive that Fab fragments might be effective as antivenoms. It certainly would be obvious to try provided there was a reasonable expectation that success would result. However, in reading Coulter et al. with a rudimentary understanding of the normal course of snake bites one would have questioned whether simultaneous intravenous administration of venom and antivenom was an acceptable model for the real life time course. As discussed above the declarations have addressed this issue and the examiner

concludes that one of ordinary skill in the art would not have had a reasonable expectation that simultaneous administration would have been reflective of real life and that there was no reasonable expectation of success. This conclusion is further supported by the evidence provided in the declarations regarding the dynamics of Fab relocalization and half-life in vivo compared to the dynamics of venom redistribution, despite the concerns raised regarding this evidence. It is further supported by the evidence presented in the declarations that the success of Fab administration needed to be evaluated in the context of what was being treated. The evidence presented on its face supported a conclusion that the success with Fab treatment was on a case by case basis. In this regard the conclusions set forth by declarants suggest that it would not have been reasonable to expect success following administration of an antivenom consisting solely of Fab fragments.

**Therefore, one of skill in the art would not have found it obvious to have prepared Fab fragments for use as an antivenom based solely on the teachings of Sullivan et al. and Coulter et al.**

But the inquiry into the obviousness of such a Fab preparation does not end here as the law of obviousness permits finding an invention obvious for reasons other than that of the inventor, *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1990).

Claim 40 could be interpreted such that the recitation of intended use does not constitute a structural limitation on the composition and therefore does not further limit the claim and that the wherein clause does not set forth a structural limitation which would distinguish it over a composition found obvious over the prior art. Granting this interpretation still does not lead to a conclusion of obviousness as is discussed below:

As noted above the invention clearly has use as a reagent in immunoassays of snake venom. This utility exists independent of their ability to neutralize venom. If such a Fab preparation had existed in the art at the time of the invention it would have been anticipated and applicant's discovery that it had neutralizing activity would not have permitted a patent on such a composition as currently claimed. But no such Fab preparation existed.

From an academic perspective one of ordinary skill in the art would have been cognizant that Fabs were utilized in immunoassays and immunohistochemistry. In this sense it would have been obvious to have made such preparations. However, such a conclusion is effectively made in a vacuum and such conclusions have not been supported as the basis for a conclusion of obviousness. Rather the conclusion must result from the perspective of the person of ordinary skill in the art at the time the invention was made. Something is not obvious merely because one recognizes that something can be done, there must be some underlying rationale. M.P.E.P. §2143.01. In this case one needs a reason more substantial than that others had employed Fabs in immunoassays or immunohistochemistry. One would start from what was known regarding immunoassays of venom components or immunohistochemical studies directed toward localizing the tissue sites which bound venom components. Nothing in the art of record nor found by the examiner in searching the immunoassay art indicates that there were problems in the immunoassay of venom components which would have lead one of ordinary skill in the art to substitute Fabs for immunoglobulins. See for example Coulter et al. (1980).

However, Coulter et al. clearly developed Fab fragments for use in immunohistochemical analysis of toxin binding to neuromuscular junctions. Their purified preparations appear to have lacked preservative and appear to be pharmaceutical compositions. Coulter prepared antisera against isolated textilotoxin and used the Fab preparation obtained therefrom for their studies. A person of ordinary skill in the art would have recognized that an alternative procedure would have been to purify textilotoxin specific antibodies from an antisera raised against intact venom through affinity chromatography on a matrix having coupled textelotoxin. Given that Sullivan et al. had prepared IgGs from antisera and that localization of venom binding sites would have been of interest one would have prepared a Fab prepration obtained therefrom to localize tissue sites which bound toxin components.

It is noted that the foregoing reasoning had not formed the basis for the previous grounds of rejection.

In conclusion, the previous grounds of rejection relying on the combined teachings of Sullivan et al. and Coulter et al. for the reasons presented therein are withdrawn. Stedman's added nothing to the rejection over Sullivan et al. and Coulter et al. and will not be discussed further.

**Extensive Evidence Would Rebut a Prima Case If One Had Been Established**  
**The claimed invention yielded unexpected, superior results**

The examiner does not find applicant's arguments persuasive for other than a composition prepared by the techniques set forth in the specification. Applicant's arguments are addressed to a particular embodiment within the scope of the claimed invention and are not commensurate in scope with the claims. Applicant prepared a Fab composition which was free of Fc contamination, but

which appeared to have some contaminating  $F(ab)_2$ . Applicant's claims embrace compositions which contain Fab but are open to the inclusion of either or both of  $F(ab)_2$  or intact IgG.

Applicant's arguments regarding the safety of  $F(ab)_2$  are noted, but not persuasive as it is not clear that the safety results are reflective of other than the impurity of the  $F(ab)_2$  preparations. Applicant's arguments that  $F(ab)_2$  could precipitate venom components is unpersuasive as intact IgG has the same property and Sullivan's earlier published results did not report such a problem. Applicant summarizes the paragraphs of the Dart Declaration concerned with the experimental results presented in the specification and argues that they are unexpected in light of the Coulter et al. article because of the superiority of the protection which resulted. However, it is not clear that the results obtained by Coulter et al. where i.v. injection was the route of administration can reasonably be compared to Applicant's results where i.p. injection was employed.

Applicant then urges that CroFab is an embodiment of the claimed invention. CroFab is a preparation of Ovine Fab fragments obtained by blending Fab fragments isolated from sheep immunized with venom from individual snake species. While the specification clearly envisions such blends it is silent with regard to using sheep as the animal source for such Fab preparations. As such there is no written description for this species of the invention in the application as originally filed. *No evidence is presented that at the time the invention was made that applicant envisioned sheep as the animal source. In addition, there is no evidence of record to support the reasoning that results obtained with horse Fab preparations would be predictive of those with Fab preparations obtained from other species.* The results described by Madaras et al. (2005) studying the

effectiveness of sheep IgG, F(ab)<sub>2</sub> and Fab directed against brown snake venom suggest that applicant's results with horse Fabs would not have been predictive of those for Fabs from other species. Leon et al.(2000) observed that sheep Fabs were not more effective than intact IgG in treatment of *Bothrops asper*.

**B. Objective evidence would rebut any prima facie case**

**1. CroFab has enjoyed great commercial success**

The evidence that CroFab has enjoyed critical success is difficult to assess. It is clear from the history of antivenoms that the field was commercially dormant at least until the time of the invention. At the time of the invention the problems with either antivenoms containing IgG or F(ab)<sub>2</sub> were known. The problems attendant to serum protein contamination and Fc antigenicity were technically resolvable at the time the invention was made. Indeed, Sullivan had prepared IgG preparations which were effective to neutralize venom. Yet, such results did not appear to induce Wyeth to develop purified IgG preparations as a clinically safer version of its ACP product. Similar arguments apply to the F(ab)<sub>2</sub> antivenoms which were commercially available at the time of the invention. It would appear that the barrier was commercial and/or regulatory. CroFab was accorded Orphan Drug status by the FDA. Reference is made to

[http://en.wikipedia.org/wiki/Orphan\\_drug](http://en.wikipedia.org/wiki/Orphan_drug) which states:

An **orphan drug** is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. The assignment of orphan status to a disease and to any drugs developed to treat it is a matter of public policy in many countries, and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics of drug research and development.

This is consistent with economic and regulatory factors as impediments to the development of more efficacious antivenoms rather than technological factors.

Had CroFab displaced an antivenom product which lacked the contaminants

present in ACP or the F(ab)<sub>2</sub> products the examiner would agree that its commercial success is objective evidence of non-obviousness.

Further in this regard is the report of the results of a Phase II study comparing CroFab to Anavip (2005). Anavip has orphan drug status and is currently in phase III clinical trials. It is a purified equine F(ab)<sub>2</sub> product. The technology existed for making such purified preparations in 1984.

Applicant urges that the adoption over ACP is striking in view of its roughly three-fold difference in price. But the argument does not set forth that cost would have been an impediment given the prevalence of malpractice suits.

Applicant's arguments concerning what CroFab was approved for as compared to ACP are noted but not persuasive. The market was clearly in need of a safer reagent and its recognition that Crofab filled that need is not surprising. If CroFab were an analytical reagent rather than a treatment reagent its success in the market place would be more determinative of non-obviousness.

## **2. CroFab has been praised by many**

It is not established that the praise results from CroFab per se rather than a product having its safety features.

Similarly, the ability to treat repeatedly would have been expected for a F(ab)<sub>2</sub> product had one existed. The Wilson comment would have applied to any available antivenom which lacked the toxicity of ACP.

There were no other commercially available products during Hurricane Katrina so it is understandable that the FDA requested additional supplies of CroFab.

## **3. CroFab satisfied a long-felt but unmet (sic)**

The examiner agrees that clinicians were aware of and dissatisfied with the commercially available antivenoms in 1984.

The examiner agrees that Sullivan et al.'s purification of IgG overcame the problem of extraneous proteins in antivenoms such as ACP. This occurred in 1982. The examiner does not agree that the problems attendant to the Fc region had not been addressed successfully until applicant's invention. There had clearly been sufficient success as there were F(ab)<sub>2</sub> antivenoms commercially available at the time of the invention. They would appear to have suffered from impurities resulting from free Fc chains. It is difficult to be definite regarding this issue as no evidence has been provided as to the purity of the F(ab)<sub>2</sub> antivenoms in 1984. The specification acknowledges them at page 4 but does not provide any further discussion nor has any product literature been provided.

### **New Grounds of Rejection**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 40-41, 56-58, 59, 61, 63-67 and 70 are rejected under 35 U.S.C. §102(a) as being clearly anticipated by Sullivan et al. (1984) which was received by the National Library of Medicine prior to the date the instant application was filed.

Sullivan (1984) teaches the production of Fab fragments from antisera obtained from equines hyperimmunized with Croatalus venom. The sera was monovalent. The antibodies were effective in preventing lethality in mice.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 42, 58, 60, 65-67, 69 and 70 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Sullivan et al. (1984) and Sullivan et al. (1982).

The teachings of Sullivan et al. (1984) are set forth above.

Sullivan et al. (1982) teaches using polyvalent IgG and additionally teaches that ACP is supplied in lyophilized form, and it is known that it results from ammonium sulfate precipitation of horse serum.

It would have been obvious to a person having ordinary skill in the art to have prepared Fabs from ACP so as to obtain a polyvalent preparation which was free of the proteins present in horse serum as well as the Fc region of Ig(G) with the expectation that the resulting preparation would not exhibit the known side effects of the antivenom.

Claims 40-42, 50, 56-60 and 63-72 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Sullivan et al. (1982) and Coulter et al. (1983) in view of the state of the art at the time the invention was made as set forth in the Dart, Russell, Sullivan and Smith declarations .

The rejection is based on the open language of independent claim 40. As currently written claim 40 includes within its scope preparations comprised of Fab fragments as well as additional components, e.g. IgG or F(ab)<sub>2</sub>.

At the time the invention was made antivenoms comprised of IgG or F(ab)<sub>2</sub> were known as well as their attendant side effects. Sullivan et al. clearly teaches that purified IgG preparations were effective in neutralizing venom and as such they would overcome many of the side effects attendant to administration of ACP. Similarly, purification of F(ab)<sub>2</sub> would yield preparations devoid of Fc chains which would reasonably be expected to reduce the effects attendant to Fc chains. At the time of the invention there existed no technological barriers to preparing such IgG or F(ab)<sub>2</sub> preparations.

Coulter et al. provides evidence that Fabs directed against one component were effective in neutralizing its toxicity when administered intravenously.

It is noted that each of the declarations speaks to the previous grounds of rejection as though limited to Fab fragments. The arguments emphasize how unexpected it was that Fab fragments would prove effective. But none of the declarants took a larger view with respect to preparations which would reasonably be expected to neutralize the effects of envenomation. Each declarant was aware of the depot effects of venom and the local tissue damage which resulted, each further recognized that Fabs could reach such sites yet each chose to emphasize the drawbacks of rapid elimination of Fabs from the circulatory system. The person of ordinary skill in the art at the time the invention was made was aware of the local and systemic effects of envenomation, and was equally aware that intravenous administration of antivenom was frequently an effective treatment. Until the publication of Coulter et al. the potential efficacy of Fabs was uncertain. Coulter et al.'s results clearly indicate that at least one component of a snake venom can protect against that components lethality when co-administered with it.

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments from either purified IgG or F(ab)<sub>2</sub> preparations and to have included them with such preparations to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream. It is recognized that venoms are complex mixtures, however, such complexity does not lead to the conclusion that the Coulter et al. results cannot be extended to venom per se. There is no evidence which supports a conclusion that Fabs generated from IgG preparations which were made against venom would not have neutralizing activity.

Claim 61 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of either (1) Sullivan et al. (1984) and Sullivan et al. (1982) as applied to claims 42, 58, 60, 65-67, 69 and 70 or (2) the combined teachings of Sullivan et al. (1982) and Coulter et al. (1983) in view of the state of the art at the time the invention was made as set forth in the Dart, Russell, Sullivan and Smith declarations as applied to claims 40-42, 50, 56-60 and 63-72 and further in view of the state of the art at the time the invention was made.

At the time the invention was made monoclonal antibodies were recognized as suitable replacements for polyclonal antibodies in therapeutic regimes. It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments of monoclonal antibodies directed against venom components as replacements for polyclonal Fab preparations.

Claim 68 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of either (1) Sullivan et al. (1984) and Sullivan et al. (1982) as applied to claims 42, 58, 60, 65-67, 69 and 70 or (2) the combined teachings of

Sullivan et al. (1982) and Coulter et al. (1983) in view of the state of the art at the time the invention was made as set forth in the Dart, Russell, Sullivan and Smith declarations as applied to claims 40-42, 50, 56-60 and 63-72 and further in view of the statement at page 4 of the specification that antivenoms directed against Bothrops were commercially available.

One of ordinary skill in the art at the time the invention was made would have found it obvious to have modified the commercially available Bothrops antivenoms to preparations containing Fabs with the expectation that such inclusion would result in a more effective antivenom preparation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59, 71 & 72 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification sets forth the concept of antivenoms comprised of Fabs and F(ab)<sub>2</sub> but does not provide any description of how such components should be assembled into a preparation which would be effective. Fabs and F(ab)<sub>2</sub>s would be expected

to compete for binding to the same sites and thus could reasonably be expected to interfere with each other's activity.

### **Observations**

The rejections relying on Sullivan et al. (1984) can be overcome with a declaration under §132 establishing that the additional authors were not inventors. However, a declaration under §131 establishing that the invention was made prior to the public disclosure of the abstract but be more appropriate assuming that the abstract was disclosed at a meeting or symposium.

The rejections relying on Coulter et al. are potentially rebuttable by establishing that at the time the invention was made it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fabs and either IgG or F(ab)<sub>2</sub>.

Resolving who the person of ordinary skill in the art at the time the invention was made is particularly challenging as it is now 26 years since the application was originally filed. Progress since 1984 appears to have been slow with regard to antivenoms comprised of IgG or F(ab)<sub>2</sub> despite the recognized problems attendant to their use as the examiner's searches indicate that such purified preparations do not appear to have been reported until the mid to late 1990s. The examiner has found nothing to indicate that the barriers to success were technological. In addition, the examiner has had a SCISEARCH done to determine if Sullivan et al.(1984), Sullivan et al. (1983), Sullivan (1987) and Russell et al. (1985) have been cited in the scientific literature. Of the foregoing only the Russell et al. (1985) has received attention. However, there are problems

with the search as Sullivan et al. (1984) and Sullivan et al. (1983) are indicated as not having been cited and yet they clearly are in Sullivan (1987).

### **Pertinent Art**

The references listed below were considered by the examiner in assessing how the field has progressed.

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**Allowable subject matter**

40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said Fab fragments neutralize the lethality of the venom of a snake of the *Crotalus* genus in the absence of IgG and F(ab)<sub>2</sub>.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael P. Woodward whose telephone number is 571-272-8373. The examiner currently works part time and can normally be reached Monday through Thursday from 9 AM to 3 PM (Eastern time). The examiner's supervisor is Gary Benzion whose telephone number is 571-272-0782.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/MP WOODWARD/  
Primary Examiner, Art Unit 1637

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| FORM PTO-1449/A and B (modified PTO/SB/08)<br><br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b> | APPLICATION NO.: 08/405,454        |  | ATTY. DOCKET NO.: P0786.70000US05 |  |
|  | FILING DATE: March 15, 1995        |  | CONFIRMATION NO.:                 |  |
|  | APPLICANT: John B. Sullivan et al. |  |                                   |  |
|  | GROUP ART UNIT: 1644               |  | EXAMINER: R. B. Schwadron         |  |
| Sheet 1 of 5   |                                    |  |                                   |  |

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\* a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 06/659,629, filed October 9, 1984 (now issued Patent No. 4,849,352), and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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